

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT



(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference SJK/BP5845276	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB00/01039	International filing date (day/month/year) 20/03/2000	Priority date (day/month/year) 18/03/1999
International Patent Classification (IPC) or national classification and IPC C07D209/08		
Applicant MEDICAL RESEARCH COUNCIL TECHNOLOGY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of 12 sheets.

3. This report contains indications relating to the following items:
- I ☒ Basis of the report.
  - II ☐ Priority
  - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - IV ☐ Lack of unity of invention
  - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - VI ☒ Certain documents cited
  - VII ☒ Certain defects in the international application
  - VIII ☒ Certain observations on the international application

Date of submission of the demand 14/09/2000	Date of completion of this report 18.04.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Hartrampf, G Telephone No. +49 89 2399 8274 

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/01039

## I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):  
**Description, pages:**

1,5-16,19-24,26, 28-50 as originally filed

2-4,17,18,25,27 as received on 17/01/2001 with letter of 12/01/2001

### Claims, No.:

1-16 as received on 17/01/2001 with letter of 12/01/2001

### Drawings, sheets:

1/7-7/7 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

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EXAMINATION REPORT**

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- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 1-3,5,6,8,9.

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 1-3,5,6,8,9.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/01039

## 1. Statement

Novelty (N)	Yes:	Claims	4,7,10-16
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	4,7,10-16
Industrial applicability (IA)	Yes:	Claims	4,7,10-16
	No:	Claims	

## 2. Citations and explanations **see separate sheet**

## VI. Certain documents cited

### 1. Certain published documents (Rule 70.10)

and / or

### 2. Non-written disclosures (Rule 70.9)

**see separate sheet**

## VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:  
**see separate sheet**

## VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**

**ad section I**

The amendments filed with the letter dated January 12, 2001 appear to be acceptable, since they do not introduce subject-matter which extends beyond the content of the application as filed, cf. Article 34(2)(b) PCT.

**ad section III**

As already indicated in the international search report, see PCT/ISA/210, claims 1 to 3, 5, 6, 8 and 9 directed to 7-nitroindoline derivatives are so broadly and ambiguously defined that a problem of clarity and conciseness arises, cf. Article 6 PCT. Furthermore there exist several contradictions between the description and the claims, e.g. several examples really made (see those bearing an indole instead of an indoline moiety) or that claims 2 and 3 are not comprised by claim 1. Due to the fact that no international search report has been established in that respect no preliminary examination has been made for said claims, cf. Rule 66.1(3) PCT.

**ad section V**

**1. PRIOR ART**

The following documents cited in the International search report were taken into consideration

D1: GOISSIS G. ET AL.: 'Synthesis of protected peptide acids and esters by photosolvolysis of 1-peptidyl-5-bromo-7-nitroindolines' PROCEEDINGS OF THE AMERICAN PEPTIDE SYMPOSIUM, vol. 5, 1977, pages 559-561

- D2: CHEMICAL ABSTRACTS, vol. 92, no. 21, 26 May 1980 Columbus, Ohio, US; abstract no. 181004x, 'Reversible blocking of acyl groups during organic synthesis using 7-nitroindoline derivatives as blocking agents' page 637; column 2; & IL 48 421 A (YEDA RESEARCH AND DEVELOPMENT CO. LTD.) 31 October 1979
- D3: PASS S. ET AL.: 'Racemization-free photochemical coupling of peptide segments' JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, US, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, vol. 103, no. 25, 1981, pages 7674-7675
- D4: ADAMS S.R. ET AL.: 'Biologically useful chelators that take up Ca<sup>2+</sup> upon illumination' JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, US, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, vol. 111, no. 20, 27 September 1989, pages 7957-7968
- D5: WO 86 00527 A (DANA-FARBER CANCER INSTITUTE INC.) 30 January 1986
- D6: CORRIE J.E.T. & TRENTHAM D.R.: 'Caged nucleotides and neurotransmitters. Chapter 5, pages 243-305. In BIOORGANIC PHOTOCHEMISTRY (MORRISON H., ed.), volume 2: 'Biological applications of photochemical switches' 1993 , JOHN WILEY & SONS, INC. , NEW YORK.

## 2. NOVELTY

Having regard to the compounds disclosed in the prior art cited above the subject-matter of the present application, i.e. the 7-nitroindoline derivatives of claim 4, appears to fulfil the requirements of novelty, cf. Article 33(2) PCT.

D1 describes 1-acyl-5-bromo-7-nitroindoline derivatives wherein the acyl group is either an amino acid or a peptide residue which may be photo released, see figure 1 on page 559.

D2 discloses 1-acyl-5-bromo-7-nitroindoline derivatives wherein the acyl group is either an aromatic-, heteroaromatic- or aliphatic carboxylic acid which may be photo released, see formula I.

D3 describes 1-acyl-5-bromo-7-nitroindoline derivatives wherein the acyl group is

either an carboxylic acid or a peptide residue which may be photo released, see reactions (1) and (2).

D4 comprises 1-acyl-5,7-dinitroindoline derivatives wherein the acyl group is a bulky chelator moiety, esp. the 1,2-bis(o-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid (BAPTA) group, see compound 1f.

D5 describes 1-acyl-7-nitroindoline derivatives wherein the acyl group is defined as -CO-W wherein "W comprises the active substance" which may be photo released, however, additionally a group Y is defined, and "Y comprises a linker and the cell binding partner", see claim 13.

D6 is a review article summarizing the biological applications of caged (photo cleavable) reagents, see *inter alia* the compound 26f on page 254 corresponding to one of the compounds of D4.

### **3. INVENTIVE STEP**

The Applicant appears to have set himself the task of making available further 1-acyl-7-nitroindolines from which carboxylic acids may be photo released in aqueous solution, see pages 1/2 of the description.

From the prior art available so far the subject-matter comprised by D1 to D4 appears to constitute the most pertinent prior art.

The solution proposed in the claims of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons.

- 3.1. As it is apparent from the application the present 1-acyl-7-nitroindoline derivatives (= caged compounds) should fulfil the following requirements
  - (i) the carboxylic acid (also being defined as bioeffector) should be released upon flash irradiation, and
  - (ii) said caged compounds should be hydrolytically stable in aqueous solution.
- 3.2. These requirements are obviously also fulfilled by the compounds described in D1, D2 and D3 which structurally differ from the present 1-acyl-7-nitroindoline derivatives by the (additional) 5-bromo substitution.

It is noted that on pages 39/40 of the present description test data of a comparison of compounds **8** and **11** are already included, demonstrating that the 5-CH<sub>2</sub>COOMe substituted compound **8** is approximately 2.5-fold more effectively photo cleaved than the corresponding 5-Br substituted compound **11**. However, from these data and also from the additional argumentation provided by the Applicant, the significance of this single comparative result with regard to all the other compounds of claim 4, bearing either no substituents in 5-position or other substituents remains entirely unclear.

- 3.3. Furthermore the chelator compounds of D4 are considered closest prior art to be compared with for the present compounds wherein the 1-acyl group is defined as a metal ion chelator group, see claims 4 and 10.

In this context it has not been clarified that in the chelator containing compounds of claim 4 the BAPTA residue has to be attached to a substituted 7-nitroindoline and not to a substituted 7-nitroindole moiety.

- 3.4. Thus claim 4 and subsequent claims do not appear to involve an inventive step as required by Article 33(3) PCT.

#### **4. INDUSTRIAL APPLICABILITY**

No objection re industrial applicability arises in so far the compounds claimed indeed show said photo cleavable properties, cf. Article 33(4) PCT.

#### **ad section VI**

PAPAGEORGIOU G. ET AL.: 'Photorelease of carboxylic acids from 1-acyl-7-nitroindolines in aqueous solution: Rapid and efficient photorelease of L-glutamate' JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, US, AMERICAN CHEMICAL SOCIETY, WASHINGTON DC, vol. 121, no. 27, 14 July 1999, pages 6503-6504 & ACS ELECTRONIC SUPPORTING INFORMATION,



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/GB00/01039

[Online] Retrieved from the Internet: <URL:http://pubs.acs.org/cgi-bin/supinfo.pl?ja990931e> [retrieved on 2000-06-09]

The priority documents pertaining to the present application were not available at the time of establishing this first written opinion. Hence, it is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the P-document cited in the international search report could become relevant to assess whether the claims satisfy the criteria set forth in Article 33(1) PCT.

**ad section VII**

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents cited in the international search report is not mentioned in the description, nor are these documents identified therein.

**ad section VIII**

1. The term "Amberlite XAD-2 resin" employed in claim 16 and appearing to be a registered trade mark has no precise meaning as it is not internationally accepted as a standard descriptive term, thereby rendering the definition of the subject-matter of said claim unclear (Article 6 PCT).

# PCT COOPERATION TREATY

PCT

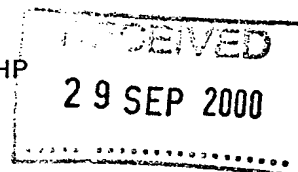
## NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU

To:

KIDDLE, Simon, J.  
Mewburn Ellis  
York House  
23 Kingsway  
London WC2B 6HP  
ROYAUME-UNI



Date of mailing (day/month/year) 21 September 2000 (21.09.00)		IMPORTANT NOTICE	
Applicant's or agent's file reference SJK/BP5845276			
International application No. PCT/GB00/01039	International filing date (day/month/year) 20 March 2000 (20.03.00)	Priority date (day/month/year) 18 March 1999 (18.03.99)	
Applicant MEDICAL RESEARCH COUNCIL et al			

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:  
AG,AU,DZ,KP,KR,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:  
AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW  
The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).
3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on  
21 September 2000 (21.09.00) under No. WO 00/55133

### REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

### REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35	Authorized officer J. Zahra Telephone No. (41-22) 338.83.38
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## INTERNATIONAL SEARCH REPORT

Int. Application No  
PCT/GB 00/01039

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C07D209/08 C07F9/09

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data, WPI Data, PAJ, CHEM ABS Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>GOISSIS G. ET AL.: "Synthesis of protected peptide acids and esters by photosolvolysis of 1-peptidyl-5-bromo-7-nitroindolines"</p> <p>PROCEEDINGS OF THE AMERICAN PEPTIDE SYMPOSIUM, vol. 5, 1977, pages 559-561, XP002037040</p> <p>the whole document</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	4,14

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

3 August 2000

Date of mailing of the international search report

24.08.00

Name and mailing address of the ISA  
European Patent Office, P.B. 5818 Patentlaan 2  
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Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax\* (+31-70) 340-3016

Authorized officer

Hartrampf, G

## INTERNATIONAL SEARCH REPORT

Inte. Application No

PCT/GB 00/01039

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEMICAL ABSTRACTS, vol. 92, no. 21, 26 May 1980 (1980-05-26) Columbus, Ohio, US; abstract no. 181004x, "Reversible blocking of acyl groups during organic synthesis using 7-nitroindoline derivatives as blocking agents" page 637; column 2; XP002144231 abstract & IL 48 421 A (YEDA RESEARCH AND DEVELOPMENT CO. LTD.) 31 October 1979 (1979-10-31) ---	4,14
Y	PASS S. ET AL.: "Racemization-free photochemical coupling of peptide segments" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, US, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, vol. 103, no. 25, 1981, pages 7674-7675, XP002037043 ISSN: 0002-7863 cited in the application reaction 2 page 7674 ---	4,14
Y	ADAMS S.R. ET AL.: "Biologically useful chelators that take up Ca <sup>2+</sup> upon illumination" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, US, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, vol. 111, no. 20, 27 September 1989 (1989-09-27), pages 7957-7968, XP000915677 cited in the application scheme I, compound 1f --- -/--	4,14

# INTERNATIONAL SEARCH REPORT

Int. Application No  
PCT/GB 00/01039

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>PAPAGEORGIOU G. ET AL.: "Photorelease of carboxylic acids from 1-acyl-7-nitroindolines in aqueous solution: Rapid and efficient photorelease of L-glutamate"</p> <p>JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, US, AMERICAN CHEMICAL SOCIETY, WASHINGTON DC, vol. 121, no. 27, 14 July 1999 (1999-07-14), pages 6503-6504, XP002144229 the whole document &amp; ACS ELECTRONIC SUPPORTING INFORMATION, 'Online!</p> <p>Retrieved from the Internet: &lt;URL:http://pubs.acs.org/cgi-bin/supinfo.pl?ja990931e&gt; 'retrieved on 2000-06-09!</p> <p style="text-align: center;">---</p>	4,7, 10-14
A	<p>WO 86 00527 A (DANA-FARBER CANCER INSTITUTE INC.) 30 January 1986 (1986-01-30) claims 1-7,13-15</p> <p style="text-align: center;">---</p>	4,7, 10-16
A	<p>CORRIE J.E.T. &amp; TRENTAM D.R.: "Caged nucleotides and neurotransmitters. Chapter 5, pages 243-305. In BIOORGANIC PHOTOCHEMISTRY (MORRISON H., ed.), volume 2: "Biological applications of photochemical switches"</p> <p>1993, JOHN WILEY &amp; SONS, INC., NEW YORK XP002144230</p> <p>cited in the application the whole document</p> <p style="text-align: center;">-----</p>	4,7, 10-16

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB 00/01039

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1-3, 5, 6, 8, 9  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-3,5,6,8,9

Present claims 1 to 3, 5, 6, 8, 9 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables and possible permutations due to the meaning of X being inter alia defined as "an effector moiety or a group capable of being coupled or converted to an effector moiety", that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely the compounds recited in the examples, i.e. those comprised by claim 4.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

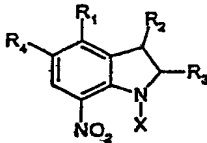
PCT/GB 00/01039

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
IL 48421	A	31-10-1979	NONE	
WO 8600527	A	30-01-1986	US 4625014 A	25-11-1986
			CA 1243015 A	11-10-1988
			DE 3582130 D	18-04-1991
			EP 0185762 A	02-07-1986
			JP 6025071 B	06-04-1994
			JP 61502608 T	13-11-1986





## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>7</sup> :</b> <b>C07D 209/08, C07F 9/09</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 00/55133</b> <b>(43) International Publication Date:</b> 21 September 2000 (21.09.00)
<b>(21) International Application Number:</b> PCT/GB00/01039 <b>(22) International Filing Date:</b> 20 March 2000 (20.03.00) <b>(30) Priority Data:</b> 9906192.1 18 March 1999 (18.03.99) GB <b>(71) Applicant (for all designated States except US):</b> MEDICAL RESEARCH COUNCIL [GB/GB]; 20 Park Crescent, London W1N 4AL (GB). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> CORRIE, John, Edgar, Thomas [GB/GB]; 17 Stockens Green, Knebworth, Hertfordshire SG3 6DG (GB). PAPAGEORGIOU, George [CY/GB]; 31 Baring Road, Barnet, Hertfordshire EN4 9AN (GB). <b>(74) Agents:</b> KIDDLE, Simon, J. et al.; Mewburn Ellis, York House, 23 Kingsway, London WC2B 6HP (GB).		<b>(81) Designated States:</b> AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> 1-ACYL-7-NITROINDOLINE DERIVATIVES, THEIR PREPARATION AND THEIR USE AS PHOTOCLEAVABLE PRECURSORS  <div style="text-align: center;">  <span style="margin-left: 20px;">(I)</span> </div>		
<b>(57) Abstract</b>  <p>Photoreleasable compounds comprising a caging moiety linked to an effector moiety represented by structural formula (I) wherein R<sub>1</sub> is hydrogen; C<sub>1-10</sub> alkyl or substituted alkyl; O(CH<sub>2</sub>)<sub>n</sub>-Y; N(COZ)(CH<sub>2</sub>)<sub>m</sub>Y; or N[(CH<sub>2</sub>)<sub>m</sub>Y'[(CH<sub>2</sub>)<sub>n</sub>Y]; R<sub>2</sub> and R<sub>3</sub> are independently selected from: hydrogen; C<sub>1-10</sub> alkyl or substituted alkyl; or R<sub>2</sub> and R<sub>3</sub> together are cycloalkyl; R<sub>4</sub> is hydrogen; C<sub>1-10</sub> alkyl or substituted alkyl; phenyl or substituted phenyl; (CH<sub>2</sub>)<sub>n</sub>Y; or (CH<sub>2</sub>)<sub>m</sub>O(CH<sub>2</sub>)<sub>n</sub>Y; wherein m and n are independently between 1 and 10; Y and Y' are independently selected from hydrogen, CO<sub>2</sub>H or salts thereof or OPO<sub>3</sub><sup>2-</sup>; Z is hydrogen or C<sub>1-10</sub> alkyl or substituted alkyl; and, X is an effector moiety or a group capable of being coupled or converted to an effector moiety, which are capable of releasing the effector moiety on irradiation, typically by flash irradiation with UV light. The photoreleasable compounds can therefore be used to deliver biologically active effector moieties such as neuroactive amino acids or metal chelators to sites where their activity is required.</p>		

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PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

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in its capacity as elected Office

<b>Date of mailing</b> (day/month/year) 18 October 2000 (18.10.00)	<b>Applicant's or agent's file reference</b> SJK/BP5845276
<b>International application No.</b> PCT/GB00/01039	<b>Priority date</b> (day/month/year) 18 March 1999 (18.03.99)
<b>International filing date</b> (day/month/year) 20 March 2000 (20.03.00)	
<b>Applicant</b> CORRIE, John, Edgar, Thomas et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
14 September 2000 (14.09.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was  
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<b>The International Bureau of WIPO</b> 34, chemin des Colombettes 1211 Geneva 20, Switzerland	<b>Authorized officer</b>  Zakaria EL KHODARY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>SJK/BP5845276</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/GB 00/ 01039</b>	International filing date (day/month/year) <b>20/03/2000</b>	(Earliest) Priority Date (day/month/year) <b>18/03/1999</b>
Applicant <b>MEDICAL RESEARCH COUNCIL</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

**4. With regard to the title,**

the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

**1-ACYL-7-NITROINDOLINE DERIVATIVES, THEIR PREPARATION AND THEIR USE AS PHOTOCLEAVABLE PRECURSORS**

**5. With regard to the abstract,**

the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.

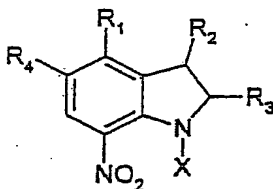


None of the figures.

## Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

Photoreleasable compounds comprising a caging moiety  
linked to an effector moiety

represented by the structural formula:



wherein

$R_1$  is hydrogen;

$C_{1-10}$  alkyl or substituted alkyl;

$O(CH_2)_nY$ ;

$N(COZ)(CH_2)_mY$ ; or

$N[(CH_2)_mY'][(CH_2)_nY]$ ;

$R_2$  and  $R_3$  are independently selected from:

hydrogen;

$C_{1-10}$  alkyl or substituted alkyl; or

$R_2$  and  $R_3$  together are cycloalkyl;

$R_4$  is hydrogen;

$C_{1-10}$  alkyl or substituted alkyl;

phenyl or substituted phenyl;

$(CH_2)_nY$ ; or

$(CH_2)_mO(CH_2)_nY$ ;

wherein:

$m$  and  $n$  are independently between 1 and 10;

$Y$  and  $Y'$  are independently selected from hydrogen,  
 $CO_2H$  or salts thereof or  $OPO_3^{2-}$ ;

$Z$  is hydrogen or  $C_{1-10}$  alkyl or substituted alkyl;

and,

$X$  is an effector moiety or a group capable of being coupled or converted to an effector moiety, which are capable of releasing the effector moiety on irradiation, typically by flash irradiation with UV light. The photoreleasable compounds can therefore be used to deliver biologically active effector moieties such as neuroactive amino acids or metal chelators to sites where their activity is required.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB 00/01039

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1-3, 5, 6, 8, 9  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-3,5,6,8,9

Present claims 1 to 3, 5, 6, 8, 9 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables and possible permutations due to the meaning of X being *inter alia* defined as "an effector moiety or a group capable of being coupled or converted to an effector moiety", that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and/or concise), namely the compounds recited in the examples, i.e. those comprised by claim 4.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

## INTERNATIONAL SEARCH REPORT

International Application No

PC 00/01039

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D209/08 C07F9/09

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data, WPI Data, PAJ, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GOISSIS G. ET AL.: "Synthesis of protected peptide acids and esters by photosolvolysis of 1-peptidyl-5-bromo-7-nitroindolines" PROCEEDINGS OF THE AMERICAN PEPTIDE SYMPOSIUM, vol. 5, 1977, pages 559-561, XP002037040 the whole document --- -/--	4, 14

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## ° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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Date of the actual completion of the international search

3 August 2000

Date of mailing of the international search report

24.08.00

Name and mailing address of the ISA

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Authorized officer

Hartrampf, G



## INTERNATIONAL SEARCH REPORT

International Application No

P B 00/01039

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEMICAL ABSTRACTS, vol. 92, no. 21, 26 May 1980 (1980-05-26) Columbus, Ohio, US; abstract no. 181004x, "Reversible blocking of acyl groups during organic synthesis using 7-nitroindoline derivatives as blocking agents" page 637; column 2; XP002144231 abstract & IL 48 421 A (YEDA RESEARCH AND DEVELOPMENT CO. LTD.) 31 October 1979 (1979-10-31) ---	4, 14
Y	PASS S. ET AL.: "Racemization-free photochemical coupling of peptide segments" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, US, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, vol. 103, no. 25, 1981, pages 7674-7675, XP002037043 ISSN: 0002-7863 cited in the application reaction 2 page 7674 ---	4, 14
Y	ADAMS S.R. ET AL.: "Biologically useful chelators that take up Ca <sup>2+</sup> upon illumination" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, US, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, vol. 111, no. 20, 27 September 1989 (1989-09-27), pages 7957-7968, XP000915677 cited in the application scheme I, compound 1f --- -/--	4, 14

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/B 00/01039

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>PAPAGEORGIOU G. ET AL.: "Photorelease of carboxylic acids from 1-acyl-7-nitroindolines in aqueous solution: Rapid and efficient photorelease of L-glutamate"</p> <p>JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, US, AMERICAN CHEMICAL SOCIETY, WASHINGTON DC, vol. 121, no. 27, 14 July 1999 (1999-07-14), pages 6503-6504, XP002144229 the whole document &amp; ACS ELECTRONIC SUPPORTING INFORMATION, 'Online!</p> <p>Retrieved from the Internet: &lt;URL:http://pubs.acs.org/cgi-bin/supinfo.pl?ja990931e&gt; 'retrieved on 2000-06-09!</p> <p>---</p>	4,7, 10-14
A	<p>WO 86 00527 A (DANA-FARBER CANCER INSTITUTE INC.) 30 January 1986 (1986-01-30) claims 1-7,13-15</p> <p>---</p>	4,7, 10-16
A	<p>CORRIE J.E.T. &amp; TRENTAM D.R.: "Caged nucleotides and neurotransmitters. Chapter 5, pages 243-305. In BIOORGANIC PHOTOCHEMISTRY (MORRISON H., ed.), volume 2: "Biological applications of photochemical switches"</p> <p>1993, JOHN WILEY &amp; SONS, INC., NEW YORK XP002144230 cited in the application the whole document</p> <p>-----</p>	4,7, 10-16

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/01039

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
IL 48421	A	31-10-1979	NONE	
WO 8600527	A	30-01-1986	US 4625014 A	25-11-1986
			CA 1243015 A	11-10-1988
			DE 3582130 D	18-04-1991
			EP 0185762 A	02-07-1986
			JP 6025071 B	06-04-1994
			JP 61502608 T	13-11-1986